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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 06/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,022	HEBBEL ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-14,45 and 46* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on May 06, 2003 has been entered as Paper No. 16.

Claims 1-14 and 45-46 are pending in the present application, and these claims have been indicated to be allowable in the Final Office Action mailed on 12/2/02 in Paper No. 11.

However, upon reconsideration, the finality of the rejection of the last Office action is withdrawn, and the indicated allowability of claims 1-14 and 45-46 is withdrawn in view of the following new ground of rejection.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Drawings

Applicant is required to submit a new set of formal drawings that reflect the correction requirement as set forth in PTO-948. Additionally, the Drawings should be labeled properly to be consistent with the Brief description of the Drawings in the specification. Examiner further notes that drawing sheets 12 and 13 are identical. Correction is required.

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application **PCT/US99/28033**, filed November 24, 1999, and Application No.

60/109,687, filed November 24, 1998. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35

U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Due to the omission of priority reference to the prior applications in the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76) within the acceptable time period, the pending claims is given a priority date of 05/24/2001.

Accordingly, following is a new ground of rejection based on the newly assigned priority date of the pending claims.

Claim Rejections - 35 USC § 103

Claims 1-2, 5-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dzau et al. (U.S. 6,352,555) in view of Asahara et al. (Science 275:964-967, 1997).

Dzau et al. teach a method for obtaining an endothelial cell culture by obtaining a sample of mononuclear cells taken from a "buffer coat" fraction of a peripheral blood sample (including human sample) and culturing the sample of mononuclear cells on a

cell adhesive polymer-coated solid support in the presence of endothelial growth factors (col. 3, lines 6-22; col. 7, lines 12-44; col. 5, lines 19-33), wherein the cell adhesive polymer is any polymer which provides a substrate for endothelial cell attachment including, without limitation, fibronectin, vitronectin, laminin, keratin, gelatin and collagen (col. 3, lines 57-61); the solid support is any solid surface which can support cell growth or differentiation including without limitation a tissue culture plate or well, bead, slide, column, bottle or other vessel (col. 4, lines 1-4); and the endothelial cell growth factors include VEGF, bFGF, IGF or any combination therefore (col. 3, lines 19-20). Dzau et al. further teach that Endothelial Growth Media supplemented with saturating concentrations of endothelial cell growth factors (VEGF, bFGF and IGF) or the endothelium cell culture medium described by Shi et al. (Blood 92:362-367, 1998) can be used for selective attachment and differentiation of early endothelial progenitor cells (none of the disclosed media contains of bovine brain extract), and that the cultures are expanded *in vitro* for a period of 10-14 days (col. 7, lines 23-44). The cell culture medium described by Shi et al. comprises 10% fetal bovine serum in M199 medium containing VEGF (10 ng/mL), bFGF (1 ng/mL) and IGF (2 ng/mL) (page 363, col. 1, bottom of first paragraph).

Drau et al. do not specifically teach that collagen type I to be coated on a solid support such as a tissue culture plate or well.

However, it is so well known in the art that type I collagen or fibronectin have been used to coat a tissue culture plate or well for an endothelial cell culture. Asahara et al. teach that putative progenitor endothelial cells isolated from human peripheral

blood (MB^{CD34+} cells) were cultured on collagen type I coated tissue culture plastic, and a limited number of cells attached, became spindle shaped and proliferated for 4 weeks (see Fig. 1B and page 964, col. 3, first full paragraph). Asahara et al. also teach that a subset of MB^{CD34+} cells plated on fibronectin-coated tissue culture plastic also promptly attached and became spindle shaped within 3 days, and the number of attaching cells in culture increased with time (see Fig. 1B).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the method taught by Dzau et al. by specifically utilizing collagen type I as a substrate for endothelial cell attachment, growth and differentiation on a solid support as it has been used in a cell culture taught by Asahara et al. One of ordinary skilled artisan would have been motivated to carry out the above modification simply because it is well known in the art that type I collagen can be used to coat a tissue culture plate or well for an endothelial cell culture.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dzau et al. (U.S. 6,352,555 with an effective filing date of 7/10/1998) in view of Asahara et al. (Science 275:964-967, 1997) as applied to claims 1-2, 5-6 and 8 above, and further in view of Levine et al. (U.S. Patent No. 5,132,223; IDS).

The combined teachings of Dzau et al. and Asahara et al. have been discussed above. However, none of the references specifically teaches that the cell culture medium comprises heparin, dextran sulfate or mixtures thereof.

However, at the effective filing date of the present application, Levine et al. teach that heparin and/or a dextran sulfate greatly potentiate the stimulatory effect of endothelial cell growth factor on the proliferation of human umbilical vein endothelial cells and of endothelial cells from adult human blood vessels (see the entire patent, particularly Brief summary of the invention).

Accordingly, it would have been obvious for an ordinary skilled artisan at the effective filing date of the present application to modify the modified method resulting from the combined teachings of Dzau et al. and Asahara et al. by further incorporating heparin and/or dextran sulfate into the cell culture medium. One of ordinary skilled artisan would have been motivated to carry out the above modification in order to attain the potentiating effects of heparin and/or dextran sulfate on the stimulatory effect of endothelial cell growth factors, for this instance VEGF, bFGF or IGF as taught by Levine et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 4-5, 7 and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dzau et al. (U.S. 6,352,555 with an effective filing date of 7/10/1998)

in view of Asahara et al. (Science 275:964-967, 1997) as applied to claims 1-2, 5-6 and 8 above, and further in view of Gupta et al. (Exp. Cell Res. 230:244-251, 1997).

The combined teachings of Dzau et al. and Asahara et al. have been discussed above. However, none of the references specifically teaches that the buffy coat cells are obtained by washing cells from a buffy coat layer obtained from human blood in cell culture medium comprising 20% human male serum or the cell culture medium containing human epidermal growth factor or hydrocorisone or human serum.

At the effective filing date of the present application, Gupta et al. already teach that microvascular endothelial cell culture medium comprising MCDB131 endothelial cell culture medium supplemented with VEGF and 20% male human serum (HUS) can be used to culture isolated human dermal microvascular endothelial cells (page 245, col. 1, third full paragraph). Gupta et al. also teach that human dermal microendothelial cells have been cultivated in a culture medium containing 30% human serum and epidermal growth factor as well as in serum-free medium containing epidermal growth factor or a culture medium containing 1 mg/ml hydrocorisone acetate with VEGF (page 245, col. 1, fourth full paragraph; page 250, bottom of col. 1). Gupta et al. further teach that VEGF stimulated the growth of human dermal microvascular endothelial cells in a dose-dependent manner in media supplemented with human serum (see abstract).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the method resulting from the combined teachings of Dzau et al. and Asahara et al. by using the cell culture medium containing 20% male human serum (HUS) taught by Gupta et al. to wash buffy coat cells obtained from

human blood as well as culturing the cells in a medium containing human serum or human epidermal growth factor or hydrocortisone.

One of ordinary skilled artisan would have been motivated to carry out the above modifications simply because the microvascular endothelial cell culture media taught by Gupta et al. are suitable for culturing endothelial cells as well as the culture media taught by Dzau et al. and Shi et al., and particularly Gupta et al. have demonstrated that VEGF stimulated the growth of human dermal microvascular endothelial cells in a dose-dependent manner in media supplemented with human serum.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dzau et al. (U.S. 6,352,555 with an effective filing date of 7/10/1998) in view of Asahara et al. (Science 275:964-967, 1997) as applied to claims 1-2, 5-6 and 8 above, and further in view of Solovey et al. (NEJM 337:1584-1590, 1997).

The combined teachings of Drau et al. and Asahara et al. have been discussed above. However, none of the references teaches that the expanded population comprises microvascular endothelial cells that are CD34+, CD36+ and expressing the P1H1 antigen.

However, Solovey et al. teach that buffy coat cells obtained from human peripheral blood contain circulating endothelial cells expressing CD36 (a distinguishing marker for microvascular endothelial cells), P1H1 antigen and CD34+ (see page 1585,

col. 1, under "identification of endothelial cells"; page 1586, col. 2, last paragraph; page 1587, col. 2, last paragraph).

Accordingly, it would have been obvious that the expanded population in the endothelial cell culture obtained from a sample of mononuclear cells taken from a "buffer coat" fraction of a peripheral blood sample (including human sample) derived from the modified method of Dzau et al. and Asahara et al. would comprise microvascular endothelial cells possessing CD34+, CD36+ and P1H1 antigen based on the teachings of Solovey et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dzau et al. (U.S. 6,352,555 with an effective filing date of 7/10/1998) in view of Asahara et al. (Science 275:964-967, 1997) as applied to claims 1-2, 5-6 and 8 above, and further in view of Dementriou et al. (U.S. Patent No. 6,140,123).

The combined teachings of Drau et al. and Asahara et al. have been discussed above. However, none of the references teaches that the cultured cells are subjected to cryopreservation or wherein the cryopreservation medium comprising fetal calf serum containing an effective amount of dimethylsuloxide or that the cryopreserved cells are thawed and culturing is resumed in the cell culture medium.

At the effective filing date of the present application, Demetriou et al. teach that cells have been routinely harvested and preserved in scientific research and

development; and when the preserved cells are to be used, they are thawed and placed in a cell culture medium. Demetriou et al. further teach that a wide used cell storage medium is DMEM containing 10 wt. % fetal calf serum and cryopreservatives such as DMSO (see cols. 1-2).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to subject the cultured cells in the modified method resulting from the combined teachings of Dzau et al. and Asahara et al. to cryopreservation as taught by Dementriou et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification for storing expanding cells for future uses or for further expansion of the cryopreserved cells in the same culture conditions at any time in the future based on the teachings of Demetriou et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on September 11, 2002 in Paper No. 10 (pages 4-6) have been fully considered.

Applicants argue mainly that the 103 art rejections are based on the Dzau et al. patent which is not a proper prior art because it has an effective filing date of July 8, 1999 whereas the present invention has the benefit of the filing date of US application 60/092,358 filed on July 10, 1998.

Applicants' argument is unpersuasive in light of the assigned priority date of 05/24/02 for the instant claims. This is due to the omission of priority reference to the prior applications in the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76) within the acceptable time period.

Conclusions

No claims are allowed.

Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER